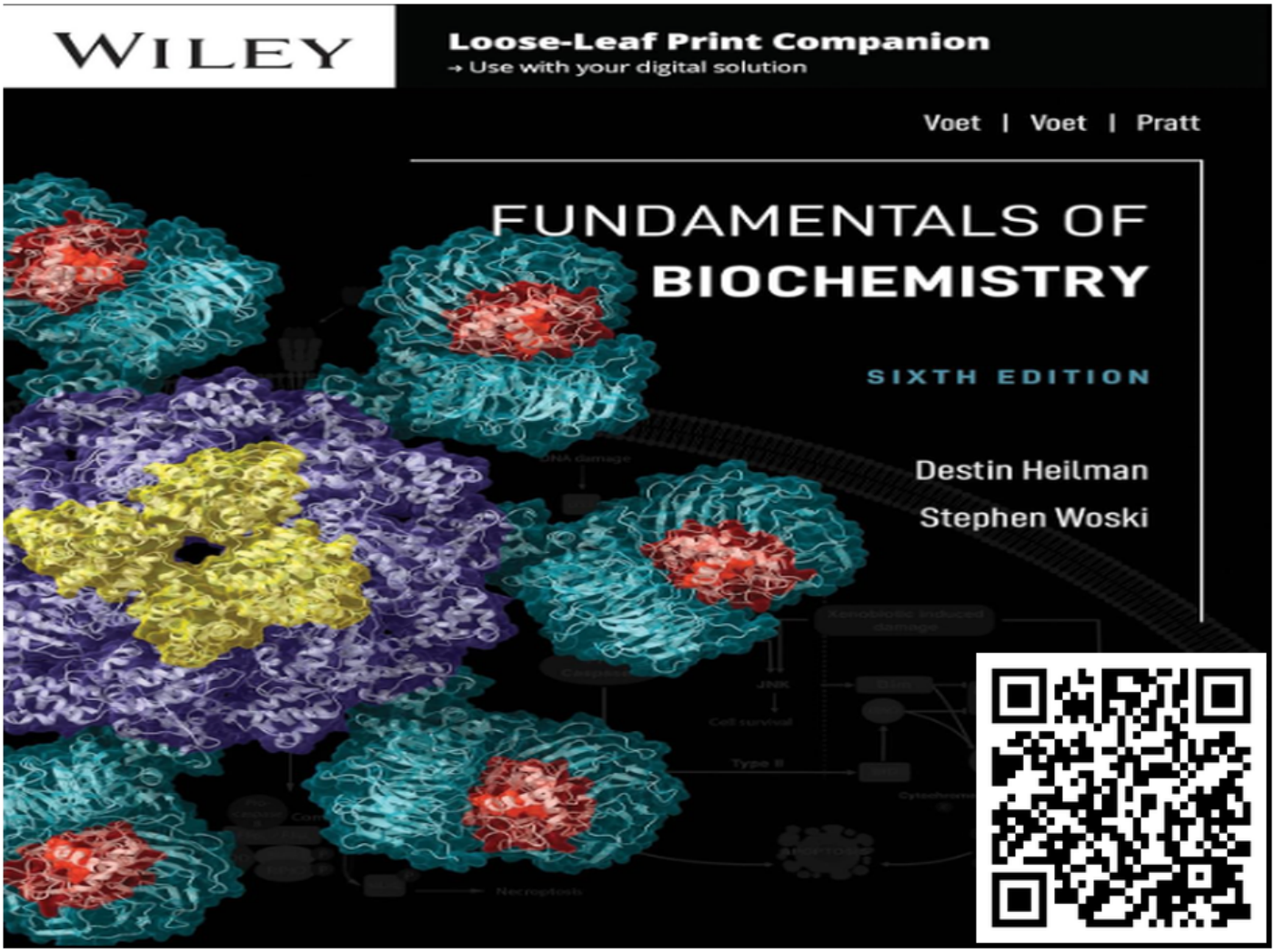

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FUNDAMENTALS OF BIOCHEMISTRY

SIXTH EDITION

Destin Heilman

Stephen Woski

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Fundamentals of Biochemistry

Life at the Molecular Level

Sixth Edition

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Dedication to Don Voet

This book owes its existence to the vision of Donald Voet, who passed away in 2023. Don's love of biochemistry and his commitment to train future biochemists originally led him to collaborate with Judith Voet to write *Biochemistry*. Don's expertise in structure and Judy's in function made them a perfect team. *Biochemistry* was a comprehensive textbook that later served as the basis for *Fundamentals of Biochemistry*. These textbooks focused not just on the myriad details of molecular structures and functions but also addressed the big ideas that Don felt were essential for conveying the beauty of biochemistry. He worked tirelessly to ensure that students would appreciate the molecular mechanisms that are common to all organisms while recognizing the importance of evolutionary variations and the power of using biochemical information to understand and solve biomedical challenges.

Don was more than a researcher and professor. He was a discerning writer with wide-ranging interests and an appetite for adventures that included extensive travel and outdoor activities of all kinds. His sense of wonder permeates his writing. Although he was thorough and exacting in his work, he never let attention to detail detract from the larger story. At the same time, he was reluctant to oversimplify or omit a detail that could reveal a subtle truth about the organization or regulation of biochemical processes. His genius was in understanding what students needed and delivering that content in a way that would be interesting and useful. He was also generous in giving credit to the researchers whose discoveries he wrote about.

Don Voet, along with Judy Voet, was highly active in the biochemical education community and earned the respect of countless instructors. Students who encountered Don and Judy at national conferences would greet them like rock stars. Even those who had never taken a biochemistry course knew about *Biochemistry*. Over the years, countless researchers needing an informative and accessible resource have made a place on their shelves for the Voets' book—work that continues to influence the professional lives of scientists worldwide.

Charlotte Pratt, Ph.D.
Seattle Pacific University
Seattle, Washington

About the Authors to the Sixth Edition

DESTIN HEILMAN received his B.S. in Microbiology/Biochemistry and Molecular Biology from Penn State University in 2000, and his Ph.D. from the University of Massachusetts Chan Medical School in 2005 under the direction of Michael R. Green. He joined the Faculty of the Worcester Polytechnic Institute in 2006 where he has taught a variety of biochemistry courses as well as introductory chemistry and analytical techniques. Motivated by the nationally renowned project-based curriculum at WPI, Dr. Heilman has engaged in extensive pedagogical innovation in both Chemistry and Biochemistry courses as well as in undergraduate capstone projects. In concert with colleagues, he spearheaded the creation of an entirely project-based general chemistry laboratory series at WPI as well as inquiry-based biochemistry laboratory courses at the capstone level. As one of the founding members of the Center for Project-Based Learning at WPI, Dr. Heilman has served as a mentor for many faculty teams from universities around the world and he routinely delivers workshops in the development of outcomes-based design of authentic projects in the classroom and laboratory. His disciplinary research focuses on the discovery and characterization of novel virus proteins that have cancer-selective toxicity. His focus on understanding these proteins has led to the development of new techniques for studying cell-selective activities and the characterization of pathways that induce programmed cell death in cancer. Leveraging his passion for teaching alongside his research, he has advised over 100 undergraduate students in his laboratory and has developed impactful pedagogical methods in integrative learning for capstone projects. Dr. Heilman has also developed and directed several local and national-level summer outreach programs including those dedicated to increasing opportunities for underrepresented students. Outside of academia, he enjoys watchmaking, woodworking, mountaineering, and gaming with his family. He is also an avid amateur astronomer and astrophotographer, and an advocate for the preservation of open land and dark skies.

STEPHEN WOSKI received his B.S. degree in Chemistry in 1986 from Emory University and his Ph.D. in 1991 from the University of Michigan under the direction of Prof. Masato Koreeda. He was then an NIH postdoctoral fellow under the supervision of Prof. Peter B. Dervan at the California Institute of Technology. Since joining the faculty of the Department of Chemistry & Biochemistry at The University of Alabama in 1994, Dr. Woski has focused on education and research at the interface between biochemistry and organic chemistry. He has taught chemistry and biochemistry courses from the introductory through graduate levels and has been involved in the creation of a new active-learning biochemistry laboratory course, a graduate literature and presentation course, and an integrated foundational core graduate course in structure and reactivity. While serving for 11 years as Director of Graduate Studies at Alabama, he actively worked to develop pipelines to broaden participation in STEM fields through involvement in the Research Experiences for Undergraduates (REU), Graduate Assistantships in Areas of National Need (GAANN), and Louis Stokes Alliance Bridge to the Doctorate programs. In research, Dr. Woski has focused on the application of the tools of synthetic organic chemistry to address problems in nucleic acid biochemistry. His research group's current active projects involve the utilization of non-natural nucleosides to examine base-base interactions in nucleic acid complexes and the structural characterization of chromium-DNA adducts to elucidate the mechanism behind chromate carcinogenicity. Dr. Woski has mentored the research of 25 doctoral and master's students and more than 80 undergraduate students. When away from campus, Dr. Woski frequently travels to locations throughout the world. There, he annoys his family by stopping to take photographs of landscapes and architecture while never missing an ancient Roman historical site.

About the Authors to the Fifth Edition

DONALD VOET received his B.S. in Chemistry from the California Institute of Technology in 1960, a Ph.D. in Chemistry from Harvard University in 1966 under the direction of William Lipscomb, and then did his postdoctoral research in the Biology Department at MIT with Alexander Rich. Upon completion of his postdoc in 1969, Don became a faculty member in the Chemistry Department at the University of Pennsylvania, where he taught a variety of biochemistry courses as well as general chemistry and X-ray crystallography. Don's research focused on the X-ray crystallography of molecules of biological interest.

JUDITH ("JUDY") VOET received her B.S. in Chemistry from Antioch College, and her Ph.D. in Biochemistry from Brandeis University under the direction of Robert H. Abeles. She was a postdoctoral researcher at the University of Pennsylvania, Haverford College, and the Fox Chase Cancer Center. Judy's main area of research involves enzyme reaction mechanisms and inhibition. She taught biochemistry at the University of Delaware before moving to Swarthmore College, where she taught biochemistry, introductory chemistry, and instrumental methods for 26 years, reaching the position of James H. Hammons Professor of Chemistry and Biochemistry. She has been a National Councilor for the American Chemical Society (ACS) Biochemistry Division and a member of the Education and Professional Development Committee of the American Society for Biochemistry and Molecular Biology (ASBMB).

Don and Judy were coauthors of four previous editions of *Fundamentals of Biochemistry* (first published in 1999) as well as four editions of *Biochemistry,* a more advanced textbook (first published in 1990). Together they were Co-Editors-in-Chief of the journal *Biochemistry and Molecular Biology Education* from 2000 to 2014. They were members of the Education Committee of the International Union of Biochemistry and Molecular Biology (IUBMB) and together, they received the 2012 award for Exemplary Contributions to Education from the ASBMB.

CHARLOTTE PRATT received her B.S. in Biology from the University of Notre Dame and her Ph.D. in Biochemistry from Duke University under the direction of Salvatore Pizzo. Although she originally intended to be a marine biologist, she discovered that biochemistry offered the most compelling answers to many questions about biological structure–function relationships and the molecular basis for human health and disease. She conducted postdoctoral research in the Center for Thrombosis and Hemostasis at the University of North Carolina at Chapel Hill. She has taught at the University of Washington and currently teaches and supervises undergraduate researchers at Seattle Pacific University. In addition to working as an editor of several biochemistry textbooks, she has co-authored *Essential Biochemistry* and previous editions of *Fundamentals of Biochemistry.*

Preface

We are delighted and deeply honored to author the *Voet, Voet, & Pratt Fundamentals of Biochemistry* for its sixth edition. As long-time users of this textbook, we cherish its focus on the structural nature of biochemistry and the depth with which the chemistry that drives life on Earth is presented. We started this project with the goal of substantively updating the prior edition while remaining faithful to the central principle that structure = function, continuing in the spirit of the previous authors. Many of the choices we have made are designed to renew the textbook for contemporary students who approach learning quite differently than in years past. Our goal is to elevate this foundational textbook to an integrative and effective learning platform for the modern biochemistry student.

Perhaps the most striking change to the textbook is a massive update to the art program, for which we have produced more than 400 new renderings of figures and graphics. These are modern, more effective renderings that better enable understanding of the subject matter. We have also included many new figures, which in large part are due to the current explosion in the number and quality of biomolecular structures. Researchers are depositing new X-ray crystallographic and NMR structures at accelerating rates. A revolution is also occurring with the development of cryoEM methods that allow for the elucidation of high resolution structures of large, multiprotein complexes. Such cryoEM techniques have also illustrated the dynamic behavior and transient species that exist in some of the most complex and amazing biochemical processes (see example Figure 25.25).

Learning biochemistry is heavily dependent on the visualization and perception of how chemistry is organized in three-dimensional space. As such, we have embedded interactive versions of molecular structures in the text to allow students to easily manipulate and better understand the complex structure of biomolecules. These interactives are integrated seamlessly into the etext; students require no additional software or instruction to make use of them. A number of videos have also been embedded in the etext that illustrate approximations of allosteric motions, highlighting the dynamic nature of protein function.

In the sixth edition, we have also focused on streamlining the student experience to better focus attention on the critical subject matter, integrating topics contextually rather than presenting them as separate elements. We have also reorganized the text to curate biochemical methods in one consolidated section, to allow the chapter material to be presented contiguously and without interruption. This provides a comprehensive, organized, and easily referenced presentation of up-to-date methods that are relevant for the modern biochemical field.

We also believe that the effectiveness of a text is not only dependent upon presenting material well but also on improved facilitation of self-assessment. Students are more successful when they are easily able to recognize what they do not understand. To streamline this process, terminal and enabling learning outcomes have been added throughout the text and these are scaffolded such that outcomes will scale with the content. For particularly critical and/or challenging learning outcomes, in-line and interactive assessments (Check Your Understanding) have been developed to provide self-assessment right where it can have the most impact. We have also identified ten challenging concepts that students find especially difficult and have targeted these with additional interactive figures, animations, and short video presentations to provide students with curated learning resources in a familiar and convenient format.

It is our hope that both students and faculty will continue to benefit from the extraordinary quality and legacy of this text and that this substantive evolution of its structure and presentation will better foster the interest and excellence of the students that have the benefit of engaging with it.

Hallmark features for this edition:

- Extensive renewal of art program that updates on modern discoveries and understanding
- Scaffolded learning outcomes that organize and facilitate student competencies
- Targeted Check Your Understanding Questions
- In-line interactive structural models
- Integration of many topics into contextualized Biochemistry in Focus sections
- Organized and updated appendix of biochemical methods
- Consolidation of topics in nucleic acid structure to better facilitate first semester outcomes
- Focus on modern search for and development of life on other worlds
- Introduction of "partially ionizable" category in amino acids
- Addition of P_{II} strand as regular secondary structure
- Reorganization and revision of catalytic mechanics
- Updates to translation mechanics and inclusion of ensemble cryoEM structures
- Consolidation of glycolytic flux into one chapter
- Reorganization of chromatin and protein-DNA interactions

What's New in the Sixth Edition

Fundamentals of Biochemistry, 6e provides a solid biochemical foundation that is rooted in chemistry while continuing in the tradition of presenting complete and balanced coverage that is clearly written and relevant to human health and disease. This edition includes new pedagogy and enhanced visuals that better adapt the text for the modern student, including a focus on enhanced self-assessment tools and scaffolding of learning outcomes throughout the text.

Key pedagogical changes:

- Scaffolded learning outcomes in each section that both streamline and elevate the effectiveness of student learning
- In-line Check Your Understanding exercises offer self-assessment where most relevant and challenge students to contextualize and combine topics
- Re-established narrative throughout the text to focus on the chemical nature of life
- Refreshed material to reinforce the integration of chemistry content
- Updated material to reflect modern discoveries and techniques in biochemistry
- Increased focus on engagement and contextual learning
- Overall art update with integrated, interactive molecular structures
- More digital resources to support 10 of the most common challenging topics for students
- Organized and updated methods section consolidates and streamlines student learning
- Contextualized Biochemistry in Focus sections add new content and accentuate understanding of the material with contextualized examples where relevant

Key changes to the Table of Contents:

- Updated Table of Contents with the number of chapters reduced
- Material involving nucleic acids, previously covered in fifth edition Chapters 3 and 24, is now in Chapter 6, a consolidated chapter on DNA structure, to better serve a first semester biochemistry curriculum
- Biomacromolecular structure are now presented as an consolidated series in Chapters 4 through 7
- Content on protein function (previously covered in the fifth edition Chapter 7), as well as newly developed content, has been presented separately and where contextually relevant in a series of new Biochemistry in Focus sections
- Topics on gluconeogenesis are now presented with glycolysis in Chapter 13
- DNA repair and recombination has been reorganized into a chapter separate from that of DNA replication (Chapters 22 and 23, respectively)
- DNA-protein interactions have been presented in context as part of regulation of gene expression in Chapter 26
- Methods content spread throughout the text has been updated and consolidated into an organized Methods Appendix

WileyPLUS Resources for Success

WileyPLUS makes it easier for you to focus on your students and easily deliver assignments that adapt to your students. With assessments you can trust, our author-branded assessment content creates a cohesive student experience. WileyPLUS allows you to meet students where they are by providing instant targeted feedback. WileyPLUS also seamlessly connects with all major learning management software systems.

Accessible resources support learners no matter their abilities.

The enriched assessment content in WileyPLUS students the opportunity to gauge their conceptual understanding and receive immediate feedback to address misconceptions.

Traditional hallmark features of WileyPLUS:

- Brief bioinformatics exercises
- Case studies
- Sample calculation videos
- Animated process diagrams
- Guided explorations
- Interactive exercises
- Test banks and lecture slides
- Answer Keys
- Image library

New to WileyPLUS for the Sixth edition:

- Interactive structural models integrated directly into the eText
- Morph animations that approximate conformational changes with many proteins
- Interactive Check Your Understanding Questions for timely self-assessment
- New WileyPlus media resources that address ten of the most difficult topics for students:
  1. Open systems and the non-equilibrium steady-state
  2. The hydrophobic effect
  3. The relationship between structure and function
  4. The relationship between primary structure and organization of R groups in 3D space
  5. Membrane dynamics and the consequences of the liquid crystalline model
  6. Energy of ES and EP, not just S and P
  7. How kinetics informs mechanics/allostery
  8. Coupled reactions and non-standard dG (pushing and pulling reactions)
  9. Coordinate control and glycolytic flux
  10. Holliday junction complex dynamics and resolution

Students and instructors will appreciate the additional resources to help them learn and teach these difficult topics.

Additional resources in WileyPLUS include assessment created around these media resources that will report to the gradebook.

Acknowledgments

We would first like to acknowledge the tremendous work and dedication that Don, Judy, and Charlotte have put into this amazing text over the years, setting the standard for biochemistry curricula. We have had the privilege of using this text for many years and have seen the tremendous impact it has had on our students and the influence it has had on biochemical pedagogy. We are honored to continue this work and to evolve this text for the next generation of students.

This edition marks a substantial update to the organization and substance of the text, and as such, has been years in the making. Along the way, we have worked with a gifted collection of colleagues who have provided their support, knowledge, and expertise in bringing the vision of this edition to fruition. Foremost, we would like to thank our team of Wiley editors, marketers, production staff, and others who played an essential role in the successful launch of this revision. In particular, we would like to thank our Developmental Editor Karen Trost, who tirelessly slogged through every word, sentence, and paragraph with us. We would also like to thank Paul Thomas (PANTHER Project) for assistance with genomics analysis, David Dixon for computational analyses, and Andrei Korostelev for lending his expertise, feedback, and ensemble cryoEM images. The excellent support team at UCSF Chimera were also critical in helping us to surmount our challenges in producing the new manipulable models, animated morphs, and hundreds of structural renderings new to this edition. Our colleagues at WPI and UA were also invaluable, and we are grateful for their help and fruitful discussions.

Finally, we would like to acknowledge our wives, Susan and Kori, our partners in life and in science. It is through their limitless patience, support, and input that our accomplishments flourish, and we are grateful to have them with us on the journey.

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One- and Three-Letter Symbols for the Amino Acids[a]

A	Ala	Alanine
B	Asx	Asparagine or aspartic acid
C	Cys	Cysteine
D	Asp	Aspartic acid
E	Glu	Glutamic acid
F	Phe	Phenylalanine
G	Gly	Glycine
H	His	Histidine
I	Ile	Isoleucine
K	Lys	Lysine
L	Leu	Leucine
M	Met	Methionine
N	Asn	Asparagine
O	Pyl	Pyrrolysine
P	Pro	Proline
Q	Gln	Glutamine
R	Arg	Arginine
S	Ser	Serine
T	Thr	Threonine
U	Sec	Selenocysteine
V	Val	Valine
W	Trp	Tryptophan
Y	Tyr	Tyrosine
Z	Glx	Glutamine or glutamic acid

[a]The one-letter symbol for an undetermined or nonstandard amino acid is X.

Thermodynamic Constants and Conversion Factors

***Joule* (J)**

$1\ J = 1\ kg \bullet m^2 \bullet s^{-2}$ $\quad 1\ J = 1\ C \bullet V$ (coulomb-volt)

$1\ J = 1\ N \bullet m$ (newton-meter)

***Calorie* (cal)**

1 cal raises temperature of 1 g of H_2O by 1 °C

$1\ cal = 4.184\ J$

***Nutritional calorie* (Cal)**

$1\ Cal = 1\ kcal$ $\quad 1\ Cal = 4184\ J$

***Avogadro's number* (N)**

$N = 6.0221 \times 10^{23}$ molecules$\bullet mol^{-1}$

***Coulomb* (C)**

$1\ C = 6.241 \times 10^{18}$ electron charges

***Faraday* ($\mathcal{F}$)**

$1\ \mathcal{F} = n$ electron charges

$1\ \mathcal{F} = 96{,}485\ C \bullet mol^{-1} = 96{,}485\ J \bullet V^{-1} \bullet mol^{-1}$

***Kelvin temperature scale* (K)**

0 K = absolute zero $\quad 273.15\ K = 0\ °C$

***Boltzmann constant* (k_B)**

$k_B = 1.3807 \times 10^{-23}\ J \bullet K^{-1}$

***Gas constant* (R)**

$R = Nk_B$ $\quad R = 1.9872\ cal \bullet K^{-1} \bullet mol^{-1}$

$R = 8.3145\ J \bullet K^{-1} \bullet mol^{-1}$ $\quad R = 0.08206\ L \bullet atm \bullet K^{-1} \bullet mol^{-1}$

The Standard Genetic Code

First Position (5′ end)	*Second Position*				*Third Position (3′ end)*
	U	C	A	G	
U	UUU Phe	UCU Ser	UAU Tyr	UGU Cys	U
	UUC Phe	UCC Ser	UAC Tyr	UGC Cys	C
	UUA Leu	UCA Ser	UAA Stop	UGA Stop	A
	UUG Leu	UCG Ser	UAG Stop	UGG Trp	G
C	CUU Leu	CCU Pro	CAU His	CGU Arg	U
	CUC Leu	CCC Pro	CAC His	CGC Arg	C
	CUA Leu	CCA Pro	CAA Gln	CGA Arg	A
	CUG Leu	CCG Pro	CAG Gln	CGG Arg	G
A	AUU Ile	ACU Thr	AAU Asn	AGU Ser	U
	AUC Ile	ACC Thr	AAC Asn	AGC Ser	C
	AUA Ile	ACA Thr	AAA Lys	AGA Arg	A
	AUG Met[a]	ACG Thr	AAG Lys	AGG Arg	G
G	GUU Val	GCU Ala	GAU Asp	GGU Gly	U
	GUC Val	GCC Ala	GAC Asp	GGC Gly	C
	GUA Val	GCA Ala	GAA Glu	GGA Gly	A
	GUG Val	GCG Ala	GAG Glu	GGG Gly	G

[a]AUG forms part of the initiation signal as well as coding for internal Met residues.

Brief Contents

Contents

CHAPTER **1**

A variety of complex organic molecules can be found in interstellar gas and dust. The large molecular clouds that give rise to stellar nurseries like those found in this image of the Cederblad 214 nebula (found in the direction of the constellation Cepheus) have been found to contain complex hydrocarbons. These include polycyclic aromatics and many smaller precursor molecules containing carbon, nitrogen, and oxygen that are important constituents of life on Earth. [Photograph by D. Heilman.]

Introduction to the Chemistry of Life

CHAPTER CONTENTS

Life on Earth arose from rather curious beginnings. Approximately 4.5 billion years ago our planet formed from a complex soup of interstellar material orbiting a relatively average, newborn dwarf star. Within that soup were precursors—complex, carbon-rich molecules with a penchant for self-assembly—which would combine and grow in complexity and versatility. This would lead to complex molecular systems that could self-replicate and in the process, iterate: a recipe for evolution. Eventually organisms would emerge capable of highly complex interactions with the environment. Extracting energy from chemical compounds or the sun, they converted this into a bewildering array of complex biomolecules from which life would continue to evolve. The Earth underwent a dramatic transition from a desolate and barren place, to a world utterly teeming with life. Through these origins, organisms on Earth have a common ancestry and therefore share the same chemical makeup; there is a single chemical theme that connects all life on this planet. We have a staggeringly diverse and wonderfully complex array of organisms to inform our understanding of life, but we are also profoundly limited in having only one version of life from which to learn. However, the Earth is not the only place where such biological precursor molecules are found. Curiously, the molecules of life are everywhere. The great cosmic spaces between the stars contain clouds of gas and dust that harbor a myriad of complex organic molecules. Ancient asteroids flung from far away worlds and comets from the outer reaches of the solar system do as well. These may have seeded life on other worlds, including our own. The Earth is but one planet among many worlds in a single solar system; it resides in a galaxy with hundreds of billions of solar systems, in a universe with hundreds of billions of galaxies. The molecules of life are everywhere. Is life then unique to Earth, or a common occurrence throughout the universe? We, who evolved from humble and curious beginnings, stand able to explore these mysteries as well as that of our own origins.

Biochemistry is the study of the chemistry of life, which describes how the properties and interactions of the vast array of biological molecules results in the amazing and diverse living systems on Earth. This chapter will discuss the potential origins of life, and the common biological forms and natural trends that are observed, all of which adhere to the same fundamental principles of chemistry and physics to which you have already been introduced. The precise point at which these systems are considered life is a subject of continuing debate, and care is taken not to apply generalizations or unduly restrict our definitions, as science continues to challenge and expand our understanding. The Earth contains a vast and diverse range of organisms that thrive in the most lush and accommodating of habitats on land and sea, but also in utterly dark, scorching, and forbidding environments where we would least expect to find life. We are continually surprised and delighted by the exotic and profound ways in which life can exist. There is much yet to be discovered both on Earth, and perhaps, on other worlds.

1.1 The Origin of Life

LEARNING OUTCOMES

After reading this section, you will be able to:

Discuss the origins and evolution of biological molecules.

- Describe the general composition of biological molecules.
- Identify the common functional groups found in biochemistry.
- Explain the chemical evolution of complex molecules from simple precursors.
- Discuss the concept of chemical complementarity and its importance in self-replication of biological polymers.

1.1A Biological Molecules Arose from Inanimate Substances

Living matter consists of a relatively small number of elements (Table 1.1). For example, C, H, O, N, P, Ca, and S account for ~97% of the dry weight of the human body (humans and most other organisms are ~70% water). Living organisms may also contain trace amounts of many other elements, including B, F, Al, Si, V, Cr, Mn, Fe, Co, Ni, Cu, Zn, As, Se, Br, Mo, Cd, I, and W, although not every organism makes use of each of these substances.

The earliest known fossil evidence of life is ~3.5 billion years old (Fig. 1.1). The preceding **prebiotic era**, which began with the formation of the earth ~4.6 billion years ago, left no direct record, but scientists can experimentally duplicate the sorts of chemical reactions that might have given rise to living organisms during that billion-year period.

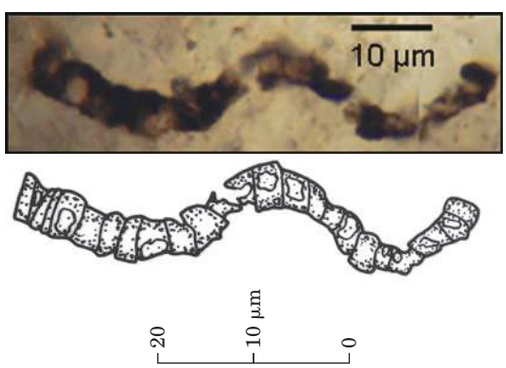
The atmosphere of the early earth probably consisted of small, simple compounds such as H_2O, N_2, CO_2, and smaller amounts of CH_4 and NH_3. In the 1920s, Alexander Oparin and J. B. S. Haldane independently suggested that ultraviolet radiation from the sun or lightning discharges caused the molecules of the primordial atmosphere to react to form simple **organic** (carbon-containing) **compounds**. This process was replicated in 1953 by Stanley Miller and Harold Urey, who subjected a mixture of H_2O, CH_4, NH_3, and H_2 to an electric discharge for about a week. Miller's analysis showed that the solution contained several amino acids (which are components of proteins) and other biochemically significant compounds. Following Miller's death in 2007, several sealed vials from the original experiment were analyzed using modern techniques, resulting in detection of over 40 different amino acids and amines. Many research groups have performed similar experiments with the benefit of modern technology and have found a multitude of complex molecules including many more amino acids, dipeptides (simple protein chains), complex cyclic hydrocarbons, and the complete palette of nucleotide bases (building blocks of DNA and RNA). Clearly, these precursors to complex biomolecules were more readily available during the formation of the Earth than previously understood.

Scientists have also suggested that early biological molecules were generated in quite a different way: in the dark and under water. Hydrothermal vents in the ocean floor, which emit solutions of metal sulfides at temperatures as high as 400 °C (Fig. 1.2), may have provided conditions

TABLE 1.1 Most Abundant Elements in the Human Body[a]

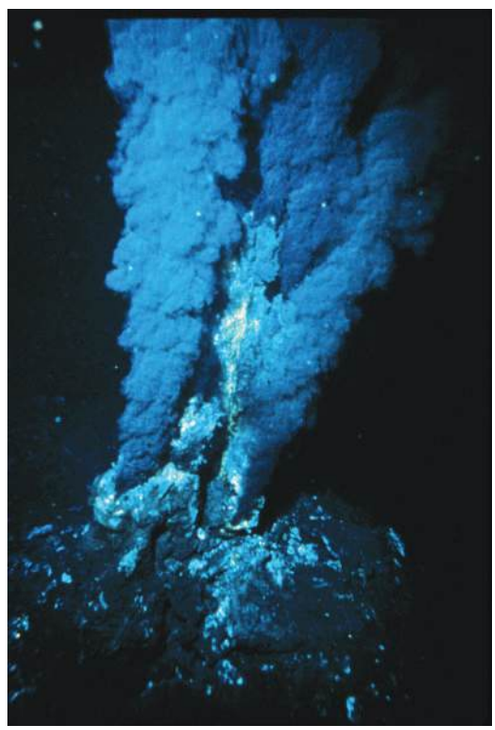
Element	Dry Weight (%)
C	61.7
N	11.0
O	9.3
H	5.7
Ca	5.0
P	3.3
K	1.3
S	1.0
Cl	0.7
Na	0.7
Mg	0.3

[a] Calculated from Frieden, E., *Sci. Am.* 227(1), 54–55 (1972).



Courtesy of J. William Schopf, UCLA

FIGURE 1.1 Microfossil of filamentous bacterial cells. This fossil (shown with an interpretive drawing) is from ~3.4-billion-year-old rock from Western Australia.



OAR / National Undersea Research Program (NURP) / NOAA / Public Domain

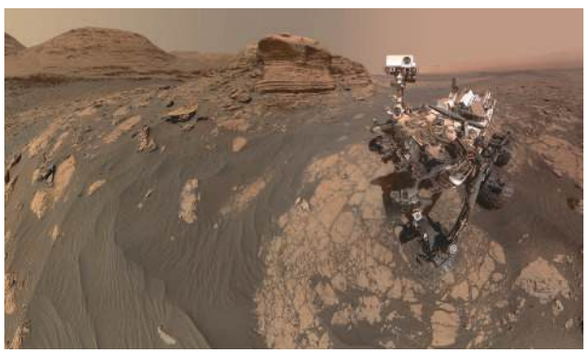
FIGURE 1.2 A hydrothermal vent. Such ocean-floor formations are known as "black smokers" because the metal sulfides dissolved in the superheated water they emit precipitate on encountering the much cooler ocean water.

suitable for the formation of amino acids and other small organic molecules from simple compounds present in seawater.

Both of these theories assume a terrestrial origin for early biological molecules, however research indicates that complex biological precursors can also form in the most distant and surprising of places. Nebulae, rich in gas and dust, are ripe with a diverse array of complex carbon compounds. Laboratory experiments conducted by NASA have produced biological precursors under conditions found only in space. Missions that have remotely sampled and analyzed the chemistry of other planets, comets, and asteroids have discovered a wealth of biological precursor molecules. Notably, researchers have found the building blocks of protein and DNA in meteor fragments that are older than the age of the solar system (**Box 1.1**). It's possible that the precursor to life on Earth was seeded from space.

Whatever their actual origin, the early organic molecules became the precursors of an enormous variety of biological molecules. These can be classified in various ways, depending on their composition and chemical reactivity. A familiarity with organic chemistry is useful for recognizing the **functional groups** (reactive portions) of molecules as well as the linkages (bonding arrangements) among them, since these features ultimately determine the biological activity of the molecules. Some of the common functional groups and linkages in biological molecules are shown in **Table 1.2**.

Box 1.1 The Search for Life on Other Worlds



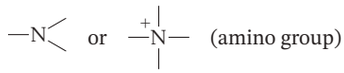
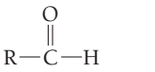
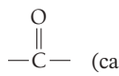
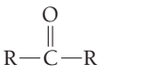
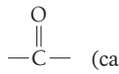
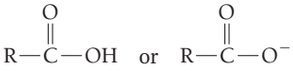
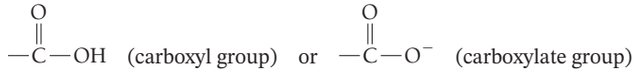
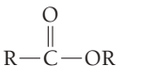
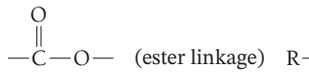
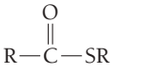
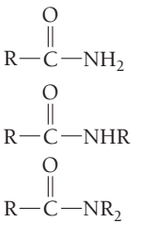
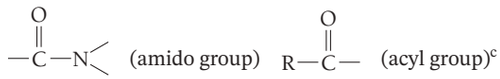
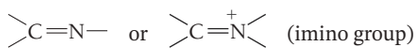
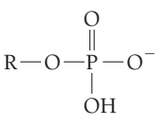
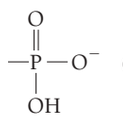
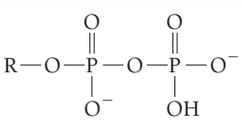
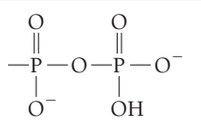
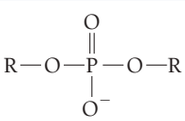
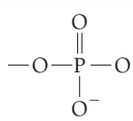
NASA /JPL-Caltech / MSSS / Public Domain

We on Earth are fortunate to have a wealth of organisms to study and understand life. However, all evidence indicates that life on Earth evolved from a common ancestor and as such, all organisms share the same origin, chemical makeup, and strict dependence on liquid water. Are these the only conditions under which life can form? Is life on Earth unique and are we the sole example in the universe? Many biochemists are preoccupied with such questions and with exploring other possible ways that life may form. The discovery of organisms on Earth that thrive in extreme conditions of temperature, pH, and salinity has changed our understanding of where life might flourish. Organisms such as extreme thermophiles survive in utter darkness where temperatures can exceed 100 °C and with pH values as low as 1.5. Many of these organisms use sulfur instead of oxygen in their metabolism and extract energy from chemical compounds instead of using photosynthesis. From the scorching interiors of volcanic fumaroles to the frozen, arid arctic tundra, organisms have adapted to these hostile environments, serving as a strong indication that we may find life existing under similar conditions on other worlds. Jupiter's moon Io is a world of volcanism, stretched and squeezed by the planet's gravity. Europa, another of Jupiter's moons, is an icy world that is likely to have a subsurface ocean warmed by geothermal energy. It is possible that life could exist on these worlds in our relative backyard where we have, and will continue to, send probes. It is also possible that life may be able to form in solvents other than water, perhaps on the liquid oceans of ethane that exist on Saturn's moon, Titan. Biochemists are studying the types of molecules and chemical strategies for life that might be possible in such a hydrophobic environment.

Exploration of our solar system is now ripe with robotic missions, many of which have the capability to identify complex molecular precursors or conditions under which life could thrive. The NASA Curiosity rover determined that liquid water as well as the chemical building blocks and nutrients needed for supporting life had been present for at least tens of millions of years on Mars. Curiosity's twin, Perseverance followed a number of years later with an enhanced mission to search for signs of ancient life. Deeper into the solar system, probes have been sent to comets and asteroids, representing early steps in studying these distant and ancient bodies. The European Space Agency (ESA) Rosetta mission was the first to orbit a comet nucleus and to land a probe (Philae) on its surface. The Japan Aerospace Exploration Agency (JAXA) successfully sampled the asteroid Ryugu and returned a capsule with material to Earth. Analysis of the material revealed precursor amino acids, complex cyclic aromatic hydrocarbons, and other carbon and nitrogen-containing compounds.

The detection of life on worlds beyond our solar system requires the use of powerful telescopes capable of detecting potentially habitable planets, and the molecular signatures of life, from great distances. NASA's Kepler mission, which surveyed over 500,000 stars in one region of our galaxy, concluded that, on average, nearly every star has at least one planet. Kepler discovered thousands of exoplanets, some of which are rocky planets in habitable zones where liquid water might exist. Missions including the James Webb Space Telescope will assist with follow-up analysis of candidate exoplanet atmospheres with spectroscopic detection of molecules from afar. Evidence gathered so far indicates that the possibility of finding life elsewhere may be much greater than we might have imagined.

TABLE 1.2 Common Functional Groups and Linkages in Biochemistry

Compound Name	Structure[a]	Functional Group or Linkage
Amine[b]	RNH_2 or $R\overset{+}{N}H_3$ R_2NH or $R_2\overset{+}{N}H_2$ R_3N or $R_3\overset{+}{N}H$	 (amino group)
Alcohol	ROH	—OH (hydroxyl group)
Thiol	RSH	—SH (sulfhydryl group)
Ether	ROR	—O— (ether linkage)
Aldehyde		 (carbonyl group)
Ketone		 (carbonyl group)
Carboxylic acid[b]		
Ester		
Thioester		
Amide		
Imine (Schiff base)[b]	R═NH or R═$\overset{+}{N}H_2$ R═NR or R═$\overset{+}{N}$HR	 (imino group)
Disulfide	R—S—S—R	—S—S— (disulfide linkage)
Phosphate ester[b]		 (phosphoryl group)
Diphosphate ester[b]		 (phosphoanhydride group)
Phosphate diester[b]		 (phosphodiester linkage)

[a] R represents any carbon-containing group. In a molecule with more than one R group, the groups may be the same or different.
[b] Under physiological conditions, these groups are ionized and hence bear a positive or negative charge.
[c] If attached to an atom other than carbon.

Question **Cover the Structure column and draw the structure for each compound listed on the left. Do the same for each functional group or linkage.**

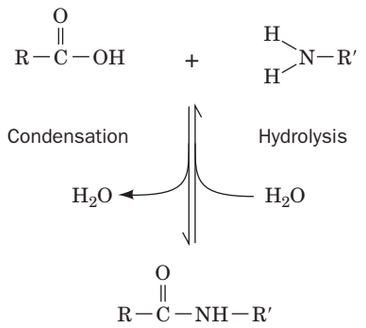


FIGURE 1.3 Reaction of a carboxylic acid with an amine. The elements of water are released during condensation. In the reverse process—hydrolysis—water is added to cleave the amide bond. In living systems, condensation reactions are not freely reversible.

TABLE 1.3 Major Biological Polymers and Their Component Monomers

Polymer	Monomer
Protein (polypeptide)	Amino acid
Nucleic acid (polynucleotide)	Nucleotide
Polysaccharide (complex carbohydrate)	Monosaccharide (simple carbohydrate)

1.1B Complex Self-Replicating Systems Evolved from Simple Molecules

Evolution During a period of chemical evolution, the prebiotic era, simple organic molecules condensed to form more complex molecules or combined end-to-end as **polymers** of repeating units. In a **condensation reaction**, the elements of water are lost. The rate of condensation of simple compounds to form a stable polymer must therefore be greater than the rate of **hydrolysis** (splitting by adding the elements of water; **Fig. 1.3**). In this prebiotic environment, minerals such as clays may have catalyzed polymerization reactions and sequestered the reaction products from water. The size and composition of prebiotic macromolecules would have been limited by the availability of small molecular starting materials, the efficiency with which they could be joined, and their resistance to degradation. The major biological polymers and their individual units (**monomers**) are given in **Table 1.3**.

Obviously, *combining different monomers and their various functional groups into a single large molecule increases the chemical versatility of that molecule*, allowing it to perform chemical feats beyond the reach of simpler molecules. (This principle of emergent properties can be expressed as "the whole is greater than the sum of its parts.") Separate macromolecules with **complementary arrangements** (reciprocal pairing) of functional groups can associate with one another (**Fig. 1.4**), giving rise to more complex molecular assemblies with an even greater range of functional possibilities.

Specific pairing between complementary functional groups permits one member of a pair to determine the identity and orientation of the other member. *Such complementarity makes it possible for a macromolecule to* **replicate**, *or copy itself, by directing the assembly of a new molecule from smaller complementary units*. Replication of a simple polymer with intramolecular complementarity is illustrated in **Fig. 1.5**. A similar phenomenon is central to the function of DNA, where the sequence of bases on one strand (e.g., A-C-G-T)

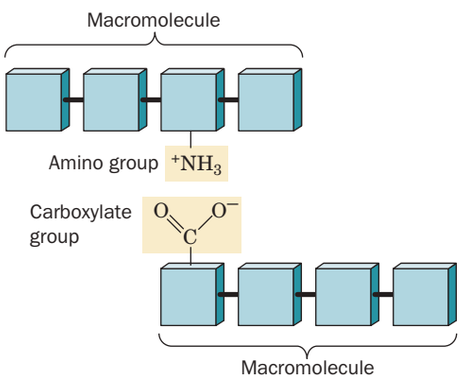


FIGURE 1.4 Association of complementary molecules. The positively-charged amino group interacts electrostatically with the negatively-charged carboxylate group.

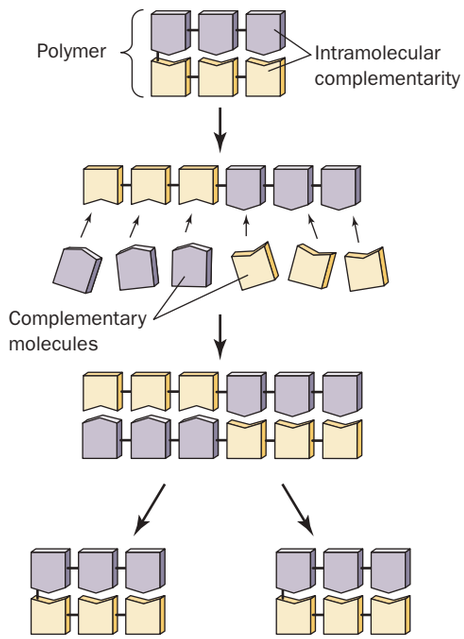


FIGURE 1.5 Replication through complementarity. In this simple case, a polymer serves as a template for the assembly of a complementary molecule, which, because of intramolecular complementarity, is an exact copy of the original.

Question Distinguish the covalent bonds from the noncovalent interactions in this polymer.

absolutely specifies the sequence of bases on the strand to which it is paired (T-G-C-A). When DNA replicates, the two strands separate and direct the synthesis of complementary daughter strands. Complementarity is also the basis for transcribing DNA into RNA and for translating RNA into protein.

A critical moment in chemical evolution was the transition from systems of randomly generated molecules to systems in which molecules were organized and specifically replicated. Once macromolecules gained the ability to self-perpetuate, the primordial environment would have become enriched in molecules that were best able to survive and multiply. The first replicating systems were no doubt somewhat sloppy, with progeny molecules imperfectly complementary to their parent molecules. Over time, **natural selection**, the competitive evolutionary process by which reproductive preference is given to the better adapted, would have favored molecules that made more accurate copies of themselves.

The "**RNA world**" hypothesis, proposed in 1962 by Alexander Rich, suggests that RNA may have served as the first self-replicating polymer. Like DNA, RNA can also store, transmit, and duplicate genetic information. However, the single-stranded nature of RNA means that this molecule can use complementarity to fold on itself into a great many structures, many having catalytic activity. The ribosome is an excellent example of an ancient catalytic RNA. According to some evolutionary sequence analyses, the ribosome may predate the evolution of the cell itself. Not unlike some modern viruses, early forms of life may have used RNA as their genome. Whether this hypothetical origin for life existed will remain unknown. Regardless, RNA serves as an excellent model system for the study of potential self-replicating systems.

GATEWAY CONCEPT
Functional Groups

Different classes of biological molecules are characterized by different types of functional groups and linkages. A biological molecule may contain multiple functional groups that facilitate interactions within and between molecules.

Checkpoint

- Which four elements occur in virtually all biological molecules?
- Summarize the major stages of chemical evolution.
- Practice drawing a simple condensation and hydrolysis reaction.
- Explain why complementarity would have been necessary for the development of self-replicating molecules.

1.2 Cellular Architecture

LEARNING OUTCOMES

After reading this section, you will be able to:

Explain how important features of cellular architecture relate to the structure and function of cells.

- Describe the advantages of compartmentation for self-replicating systems.
- Define metabolic pathways and explain the reasoning for their development in organisms.
- Compare the general features of the two major types of cells.
- Describe features of each of the three evolutionary domains of organisms.
- Explain the theory of endosymbiosis and the origin of eukaryotes.
- Outline the four principles of evolution and provide examples of each using modern organisms.

The types of systems described so far would have had to compete for available resources with all of the other components of the primordial Earth. A system that was sequestered and protected by boundaries of some sort would have a selective advantage. How these boundaries first arose, or even what they were made from, is obscure. One theory is that membranous **vesicles** (fluid-filled sacs) first attached to and then enclosed self-replicating systems. These vesicles would have become the first cells.

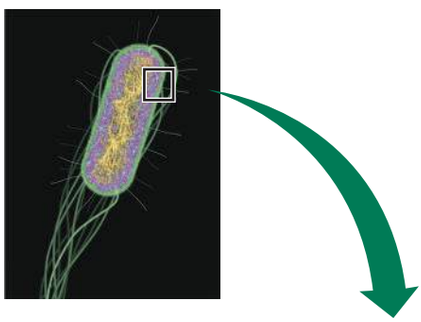
1.2A Cells Carry Out Metabolic Reactions

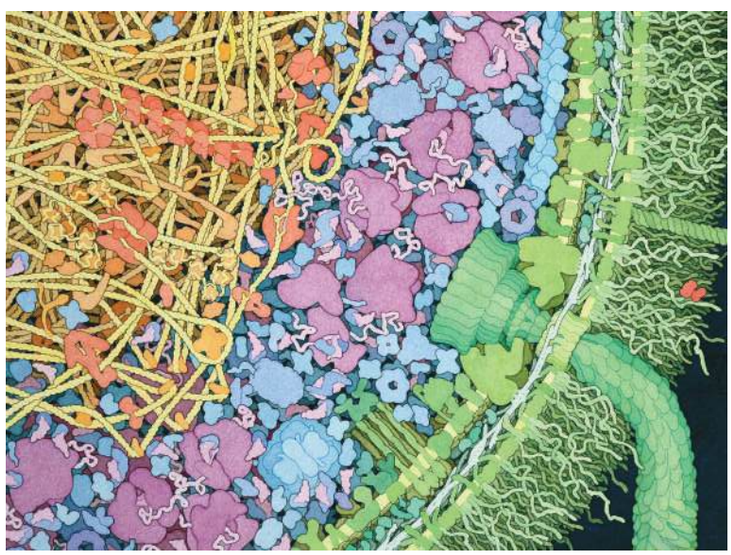
There are several advantages to **compartmentation**. In addition to receiving some protection from adverse environmental forces, an enclosed system can maintain high local concentrations of components that would otherwise diffuse away. More concentrated substances can react more readily, leading to increased efficiency in polymerization and other types of chemical reactions.

A membrane-bound compartment that protected its contents would gradually become quite different in composition from its surroundings. Modern cells contain high concentrations of ions, small molecules, and large molecular aggregates that are found only in traces—if at all—outside the cell. For example, a cell of the bacterium ***Escherichia coli* (*E. coli*)** contains millions of molecules, representing some 3000 to 6000 different compounds (**Fig. 1.6**). A typical animal cell may contain 100,000 different types of molecules.

Early cells depended on the environment to supply building materials. As some of the essential components in the prebiotic soup became scarce, natural selection favored organisms that developed **metabolic pathways**, mechanisms for synthesizing the required compounds from simpler but more abundant **precursors**. The first metabolic reactions may have used metal or clay **catalysts** (substances that promote chemical reactions without undergoing a net change). In fact, metal ions are still at the heart of many chemical reactions in modern cells. Some catalysts may also have arisen from polymeric molecules with the appropriate functional groups.

In general, biosynthetic reactions require energy; hence the first cellular reactions also would have needed an energy source. The eventual depletion of preexisting energy-rich substances in the prebiotic environment would have favored the development of energy-producing metabolic pathways. For example, photosynthesis evolved relatively early to take advantage of a practically inexhaustible energy supply, the sun. However, the accumulation of O_2 generated from H_2O by photosynthesis (the modern atmosphere is 21% O_2) presented an additional challenge to organisms adapted to life in an oxygen-poor atmosphere. Metabolic refinements eventually permitted organisms not only to avoid oxidative damage but also to use O_2 for oxidative metabolism, a much more efficient form of energy metabolism than anaerobic metabolism. Vestiges of ancient life can be seen in the anaerobic metabolism of certain modern organisms.





From Goodsell, D.S., *The Machinery of Life* (2nd ed.), Springer (2009). Reproduced with permission.

FIGURE 1.6 Cross-section through an *E. coli* cell. The cytoplasm is packed with macromolecules. At this magnification (~1,000,000×), individual atoms are too small to resolve. The green structures on the right include the inner and outer membrane components along with a portion of a flagellum. Inside the cell, various proteins are shown in blue, and ribosomes are purple. The gold and orange structures represent DNA and DNA-binding proteins, respectively. In a living cell, the remaining spaces would be crowded with water and small molecules.

Early organisms that developed metabolic strategies to synthesize biological molecules, conserve and utilize energy in a controlled fashion, and replicate within a protective compartment were able to propagate in an ever-widening range of habitats. Adaptation of cells to different external conditions ultimately led to the present diversity of species. Specialization of individual cells also made it possible for groups of differentiated cells to work together in multicellular organisms.

1.2B There Are Two Types of Cells: Prokaryotes and Eukaryotes

There are two major classifications of cells: the **eukaryotes** (Greek: *eu*, good or true + *karyon*, kernel or nut), which have a membrane-enclosed **nucleus** encapsulating their DNA; and the **prokaryotes** (Greek: *pro*, before), which lack a nucleus. *Prokaryotes, comprising the various types of bacteria, have relatively simple structures and are almost all unicellular* (although they may form filaments or colonies of independent cells). *Eukaryotes, which can be multicellular or unicellular, are vastly more complex than prokaryotes.*

Prokaryotes are the most numerous and widespread organisms on the earth. This is because their varied and often highly adaptable metabolisms are well-suited to an enormous variety of habitats. Prokaryotes range in size from 1 to 10 μm and have one of three basic shapes (**Fig. 1.7**): spheroidal (cocci), rodlike (bacilli), and helically coiled (spirilla). Except for an outer cell membrane, which in most cases is surrounded by a protective cell wall, nearly all prokaryotes lack cellular membranes. However, the prokaryotic **cytoplasm** (cell contents) is by no means a homogeneous soup. Different metabolic functions are carried out in different regions of the cytoplasm (Fig. 1.6). The best characterized prokaryote is *Escherichia coli*, a 2 μm by 1 μm rodlike bacterium that inhabits the mammalian colon.

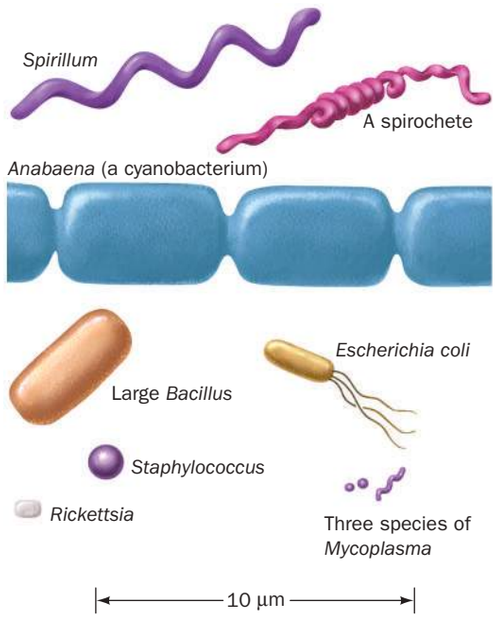


FIGURE 1.7 **Scale drawings of some prokaryotic cells.**

Eukaryotic cells are generally 10 to 100 μm in diameter and thus have a thousand to a million times the volume of typical prokaryotes. However, it is not size, but a profusion of membrane-enclosed **organelles** that best characterizes eukaryotic cells (**Fig. 1.8**). In addition to a nucleus, eukaryotes have an **endoplasmic reticulum**, the site of synthesis of many cellular components, some of which are subsequently modified in the **Golgi apparatus**. The bulk of aerobic metabolism takes place in **mitochondria** in almost all eukaryotes, and photosynthetic cells contain **chloroplasts**, which convert the energy of the sun's rays to chemical energy. Other organelles, such as **lysosomes** and **peroxisomes**, perform specialized functions. **Vacuoles**, which are more prominent in plant than in animal cells, usually function as storage depots. The **cytosol** (the cytoplasm minus its membrane-bound organelles) is organized by the **cytoskeleton**, an extensive array of filaments that also gives the cell its shape and the ability to move.

The various organelles that compartmentalize eukaryotic cells represent a level of complexity that is largely lacking in prokaryotic cells. Nevertheless, prokaryotes are more efficient than eukaryotes in many respects. Prokaryotes have exploited the advantages of simplicity and miniaturization. Their rapid growth rates permit them to occupy ecological niches in which there may be drastic fluctuations of the available nutrients. In contrast, the complexity of eukaryotes renders them larger and more slowly growing than prokaryotes, giving them the competitive advantage in stable environments with limited resources. It is therefore erroneous to consider prokaryotes as evolutionarily primitive compared to eukaryotes. Both types of organisms are well adapted to their respective lifestyles.

1.2C Molecular Data Reveal Three Evolutionary Domains of Organisms

Evolution The practice of lumping all prokaryotes in a single category based on what they lack—a nucleus—obscures their metabolic diversity and evolutionary history. Conversely, the remarkable morphological diversity of eukaryotic organisms (consider the anatomical differences

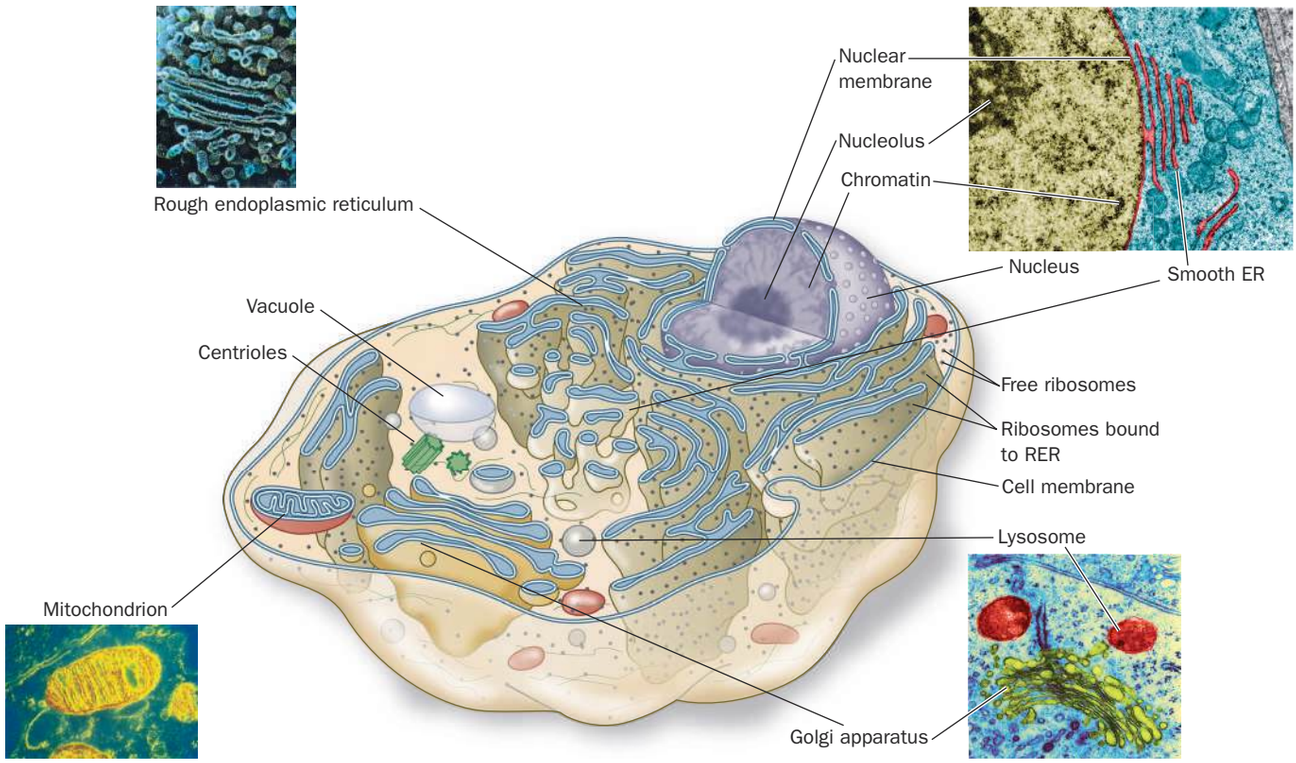


FIGURE 1.8 Diagram of a typical animal cell with electron micrographs of its organelles. Membrane-bound organelles include the nucleus, endoplasmic reticulum, lysosome, peroxisome (not pictured), mitochondrion, vacuole, and Golgi apparatus. The nucleus contains chromatin (a complex of DNA and protein) and the nucleolus (the site of ribosome synthesis). The rough endoplasmic reticulum is studded with ribosomes; the smooth endoplasmic reticulum is not. A pair of centrioles help organize cytoskeletal elements. A typical plant cell differs mainly by the presence of an outer cell wall and chloroplasts in the cytosol.

[Nucleus and Smooth endoplasmic reticulum JOSE LUIS CALVO MARTIN & JOSE ENRIQUE GARCIA-MAURIÑO MUZQUIZ / Getty Images; rough endoplasmic reticulum Professors Pietro M. Motta & Tomonori Naguro / Science Source; mitochondrion CNRI/Science Source; Golgi apparatus and Lysosome Science Source.]

Question With the labels covered, name the parts of this eukaryotic cell.

among, say, an amoeba, an oak tree, and a human being) masks their fundamental similarity at the cellular level. Traditional taxonomic schemes (**taxonomy** is the science of biological classification), which are based on gross morphology, have proved inadequate to describe the actual relationships between organisms as revealed by their evolutionary history (**phylogeny**).

Biological classification schemes based on reproductive or developmental strategies more accurately reflect evolutionary history than those based solely on adult morphology. However, *phylogenetic relationships are best deduced by comparing polymeric molecules—RNA, DNA, or protein—from different organisms*. For example, analysis of RNA led Carl Woese to group all organisms into three domains (**Fig. 1.9**). The **archaea** (also known as **archaebacteria**) are a group of prokaryotes that are as distantly related to other prokaryotes (the **bacteria**, sometimes called **eubacteria**) as both groups are to eukaryotes (**eukarya**). The archaea include some unusual organisms: the **methanogens** (which produce CH_4), the **halobacteria** (which thrive in concentrated brine solutions), and certain **thermophiles** (which inhabit hot springs). The pattern of branches in Woese's diagram indicates the divergence of different types of organisms (each branch point represents a common ancestor). The three-domain scheme also shows that animals, plants, and fungi constitute only a small portion of all life forms. Such phylogenetic trees supplement the fossil record, which provides a patchy record of life prior to about 600 million years before the present (multicellular organisms arose about 700–900 million years ago).

It is unlikely that eukaryotes are descended from a single prokaryote, because the differences among eubacteria, archaea, and eukaryotes are so profound. Instead, eukaryotes probably

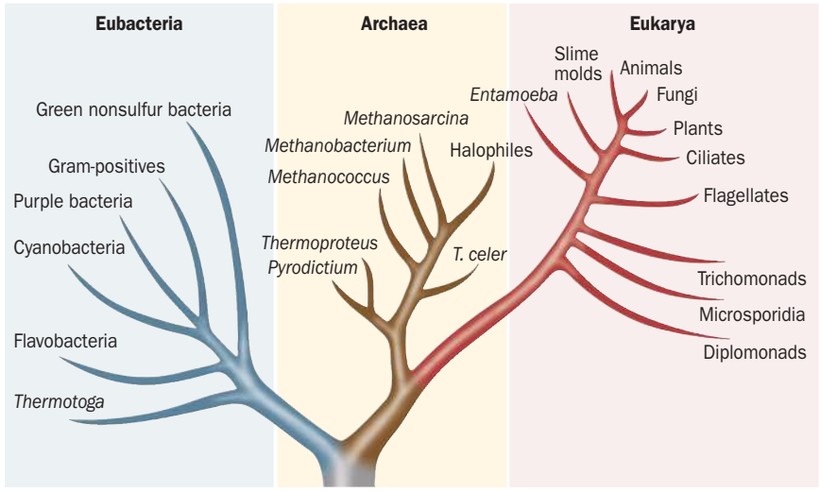


FIGURE 1.9 Phylogenetic tree showing the three domains of organisms. The branches indicate the pattern of divergence from a common ancestor. The archaea are prokaryotes, like eubacteria, but share many features with eukaryotes.

Source: Adapted from Wheelis, M.L., Kandler, O., and Woese, C.R. *Proc. Natl. Acad. Sci.* 89, 2931 (1992).

evolved from the association of archaebacterial and eubacterial cells. The eukaryotic genetic material includes features that suggest an archaebacterial origin. In addition, the mitochondria and chloroplasts of modern eukaryotic cells resemble eubacteria in size and shape, and both types of organelles contain their own genetic material and protein synthetic machinery, with some unique differences in the genetic code from that of the nucleus. Evidently, as Lynn Margulis proposed, mitochondria and chloroplasts evolved from free-living eubacteria that formed **symbiotic** (mutually beneficial) relationships with a primordial eukaryotic cell (**Box 1.2**). In fact, certain eukaryotes that lack mitochondria or chloroplasts permanently harbor symbiotic bacteria.

1.2D Organisms Continue to Evolve

Evolution The natural selection that guided prebiotic evolution continues to direct the evolution of organisms. Richard Dawkins has likened evolution to a blind watchmaker capable of producing intricacy by accident, although such an image fails to convey the vast expanse of time and the incremental, trial-and-error manner in which complex organisms emerge. Small **mutations** (changes in an individual's genetic material) arise at random as the result of chemical damage or inherent errors in the DNA replication process. *A mutation that increases the chances of survival of the individual increases the likelihood that the mutation will be passed on to the next generation*. Beneficial mutations tend to spread rapidly through a population; deleterious changes tend to die along with the organisms that harbor them.

The theory of evolution by natural selection, which was first articulated by Charles Darwin in the 1860s, has been confirmed through observation and experimentation. It is therefore useful to highlight several important—and often misunderstood—principles of evolution:

1. *Evolution is not directed toward a particular goal.* It proceeds by random changes that may affect the ability of an organism to reproduce under the prevailing conditions. An organism that is well adapted to its environment may fare better or worse when conditions change.
2. *Variation among individuals* allows organisms to adapt to unexpected changes. This is one reason that genetically homogeneous populations (e.g., a corn crop) are so susceptible to a single challenge (e.g., a fungal blight). A more heterogeneous population is more likely to include individuals that can resist the adverse.
3. *The past determines the future.* New structures and metabolic functions emerge from preexisting elements. For example, insect wings did not erupt spontaneously but appear to have developed gradually from small heat-exchange structures.
4. *Evolution is ongoing,* although it does not proceed exclusively toward complexity. An anthropocentric view places human beings at the pinnacle of an evolutionary scheme, but a quick survey of life's diversity reveals that simpler species have not died out or stopped evolving.

Box 1.2 Pathways of Discovery

Lynn Margulis and the Theory of Endosymbiosis

Cavan Images/Alamy Stock Photo

Lynn Margulis (1938–2011) After growing up in Chicago and enrolling in the University of Chicago at age 16, Lynn Margulis intended to be a writer. Her interest in biology was sparked by a required science course for which she read Gregor Mendel's accounts of his experiments with the genetics of pea plants. Margulis continued her studies at the University of Wisconsin–Madison and at the University of California, Berkeley, earning a doctorate in 1963. Her careful consideration of cellular structures led her to hypothesize that eukaryotic cells originated from a series of endosymbiotic events involving multiple prokaryotes. The term *endo* (Greek: within) refers to an arrangement in which one cell comes to reside inside another. This idea was considered outrageous at the time (in 1967), but many of Margulis's ideas have since become widely accepted.

Endosymbiosis as an explanation for the origin of mitochondria had been proposed by Ivan Wallin in 1927, who noted the similarity between mitochondria and bacteria in size, shape, and cytological staining. Wallin's hypothesis was rejected as being too fantastic and was ignored until it was taken up again by Margulis. By the 1960s, much more was known about mitochondria (and chloroplasts), including the facts that they contained DNA and reproduced by division. Margulis did not focus all her attention on the origin of individual organelles; instead, she sought to explain the origin of the entire eukaryotic cell, which also includes centrioles, another possible bacterial relic. Her paper, "On the origin of mitosing cells," was initially rejected by several journals before being accepted by the *Journal of Theoretical Biology*. The notion that a complex eukaryotic cell could arise from a consortium of mutually dependent prokaryotic cells was incompatible with the prevailing view that evolution occurred as a series of small steps. Evolutionary theory of the time had no room for the dramatic amalgamation of cells—and their genetic material—that Margulis had proposed. Nevertheless, the outspoken Margulis persisted, and by the time she published *Symbiosis in Cell Evolution* in 1981, much of the biological community had come on board to agree with her.

Two main tenets of Margulis's theory are now almost universally accepted: (1) mitochondria are the descendants of oxygen-respiring bacteria, and (2) chloroplasts were originally photosynthetic bacteria. The third, the idea that the eukaryotic cytoplasm is the remnant of an archaebacterial cell, is still questioned by some biologists. Margulis was in the process of collecting evidence to support a fourth idea, that cilia and flagella and some sensory structures such as the light-sensing cells of the eye are descendants of free-living spirochete bacteria. Margulis's original prediction that organelles such as mitochondria could be isolated and cultured has not been fulfilled. However, there is ample evidence for the transfer of genetic material between organelles and the nucleus, consistent with Margulis's theory of endosymbiosis. In fact, current theories of evolution include the movement of genetic material among organisms, as predicted by Margulis, in addition to small random mutations as agents of change.

Perhaps as an extension of her work on bacterial endosymbiosis, Margulis came to recognize that the interactions among many different types of organisms as well as their interactions with their physical environment constitute a single self-regulating system. This notion is part of the Gaia hypothesis proposed by James Lovelock, which views the entire earth as one living entity (Gaia was a Greek earth goddess). However, Margulis had no patience with those who sought to build a modern mythology based on Gaia. She was adamant about the importance of using scientific tools and reasoning to discover the truth and was irritated by the popular belief that humans are the center of life on earth. Margulis understood that human survival depends on our relationships with waste-recycling, water-purifying, and oxygen-producing bacteria, with whom we have been evolving, sometimes endosymbiotically, for billions of years.

Sagan, L., On the origin of mitosing cells, *J. Theor. Biol.* 14, 255–274 (1967).

Checkpoint

- Explain the selective advantages of compartmentation and metabolic pathways.
- Discuss the differences between prokaryotes and eukaryotes.
- List the major eukaryotic organelles and their functions.
- Explain why a taxonomy based on molecular sequences is more accurate than one based on morphology.
- Which of the three domains are prokaryotic? Which domain is most similar to eukaryotes?
- Explain how individual variations allow evolution to occur.
- Why is evolutionary change constrained by its past but impossible to predict?

1.3 Thermodynamics

LEARNING OUTCOMES

After reading this section, you will be able to:

Distinguish the first and second laws of thermodynamics.

- Relate the concept of enthalpy to the first law of thermodynamics.
- Relate the concept of entropy to the second law of thermodynamics.
- Define free energy and spontaneity and relate the two for any process.
- Explain how the sign of enthalpy or entropy will affect the spontaneity of a process.
- Define state functions and biochemical standard state.
- Calculate the free energy of a chemical reaction under standard and non-standard conditions.
- Explain the non-equilibrium steady state and its relationship to living systems.

The normal activities of living organisms demand an almost constant input of energy. Even at rest, organisms devote a considerable portion of their biochemical apparatus to the acquisition and utilization of energy. The study of energy and its effects on matter falls under the purview of thermodynamics (Greek: *therme*, heat + *dynamis*, power). Although living systems present some practical challenges to thermodynamic analysis, *life obeys the laws of thermodynamics*. Understanding thermodynamics is important not only for describing a particular process—such as a biochemical reaction—in terms that can be quantified, but also for predicting whether that process *can* actually occur. To begin, this section will review the fundamental laws of thermodynamics. It will then turn your attention to free energy and how it relates to chemical reactions. Finally, we will look at how biological systems deal with the laws of thermodynamics.

1.3A The First Law of Thermodynamics States That Energy Is Conserved

In thermodynamics, a **system** is defined as the part of the universe that is of interest, such as a chemical reaction or an organism; the rest of the universe is known as the surroundings. The system has a certain amount of **energy, *E***. *The first law of thermodynamics states that total energy of the universe is constant and that energy can be neither created nor destroyed during any physical or chemical process.* This means that when the system undergoes a change, some of its energy can be transferred or change form, but it cannot be consumed. For example, the energy stored in chemical bonds can be converted to kinetic energy to perform work. Energy can be used to perform different kinds of work and it is useful to speak of energy in specific forms, such as mechanical energy, electrical energy, or chemical energy—all of which are relevant to living systems.

The change that occurs in the internal energy of a system (ΔE) corresponds to the sum of the heat transferred (q) and work done (w):

$$\Delta E = q + w \tag{1.1}$$

where the upper case Greek letter Δ (delta) indicates change. For many chemical systems, w is defined by pressure-volume work ($w = -P\Delta V$), especially where large amounts of gas are produced, increasing the volume. However, for most biological processes we are not concerned with pressure-volume work as volume changes are typically insignificant.

$$\Delta E = q - P\Delta V = q_v \tag{1.2}$$

In open systems, these processes are typically at constant pressure. Under such conditions q is equivalent to a thermodynamic quantity called **enthalpy** (Greek: *enthalpein*, to warm in), symbolized H, with the following relationship:

$$\Delta E = \Delta H - P\Delta V \tag{1.3}$$

Enthalpy refers to the heat *content* of a system. Since you already know that volume changes in most biological processes are insignificant, you can see that under conditions of constant pressure, the energy change for the reacting system is equivalent to its enthalpy change and thus, q:

$$\begin{aligned} \Delta E &= \Delta H - P\Delta V = q_p + w \\ \Delta E &= \Delta H - 0 = q_p + 0 \\ \Delta E &= \Delta H = q_p \end{aligned} \tag{1.4}$$

Enthalpy, like energy, heat, and work, is given units of joules. Some commonly used units, biochemical constants, and other conventions are given in **Box 1.3**.

Thermodynamics is useful for indicating the **spontaneity** of a process; a determination of whether the process *can* occur (regardless of whether a process *will* occur). A spontaneous process occurs without the input of additional energy from outside the system (although keep in mind that thermodynamic spontaneity has nothing to do with how quickly a process occurs). However, the first law of thermodynamics cannot by itself determine whether a process is spontaneous. Consider two objects of different temperatures that are brought together. Heat flows spontaneously from the warmer object to the cooler one, never vice versa, yet heat flow in either direction would be consistent with the first law of thermodynamics since the aggregate energy of the two objects would not change. Therefore, heat alone (enthalpy in this case) is not enough to determine spontaneity; an additional thermodynamic parameter is needed.

Box 1.3 Perspectives in Biochemistry

Biochemical Conventions

Modern biochemistry generally uses Système International (SI) units, including meters (m), kilograms (kg), and seconds (s) and their derived units, for various thermodynamic and other measurements. The following lists the commonly used biochemical units, some useful biochemical constants, and a few conversion factors.

Units		
Energy, heat, work	joule (J)	$kg \cdot m^2 \cdot s^{-2}$ or $C \cdot V$
Electric potential	volt (V)	$J \cdot C^{-1}$

Prefixes for units			
mega (M)	10^6	nano (n)	10^{-9}
kilo (k)	10^3	pico (p)	10^{-12}
milli (m)	10^{-3}	femto (f)	10^{-15}
micro (μ)	10^{-6}	atto (a)	10^{-18}

Conversions	
angstrom (Å)	10^{-10} m
calorie (cal)	4.184 J
kelvin (K)	degrees Celsius (°C) + 273.15

Constants	
Avogadro's number (N)	6.0221×10^{23} molecules$\cdot$mol^{-1}
Coulomb (C)	6.241×10^{18} electron charges
Faraday (F)	96,485 C$\cdot$mol^{-1} or 96,485 J$\cdot$V$^{-1}\cdot$mol^{-1}
Gas constant (R)	8.3145 J$\cdot$K$^{-1}\cdot$mol^{-1}
Boltzmann constant (k_B)	1.3807×10^{-23} J$\cdot$K^{-1}(R/N)
Planck's constant (h)	6.6261×10^{-34} J$\cdot$s

Throughout this text, molecular masses of particles are expressed in units of **daltons (Da)**, which are defined as 1/12th the mass of a ^{12}C atom (1000 Da = 1 **kDa**). Biochemists also use molecular weight, a dimensionless quantity defined as the ratio of the particle mass to 1/12th the mass of a ^{12}C atom, which is symbolized M_r (for relative molecular mass).